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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup>:</b> <b>C07D 235/18, A61K 31/415,</b> <b>A61P 7/02, (continued on the following page)</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/35886</b> <b>(43) International Publication Date:</b> 22 June 2000 (22.06.00)
<b>(21) International Application Number:</b> PCT/US99/30302 <b>(22) International Filing Date:</b> 17 December 1999 (17.12.99) <b>(30) Priority Data:</b> 60/113,007 18 December 1998 (18.12.98) US <b>(71) Applicant (for all designated States except US):</b> AXYS PHARMACEUTICALS, INC. [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ALLEN, Darin, Arthur [US/US]; 519 Sierra Vista #3, Mountain View, CA 94043 (US). HATAYE, Jason, M. [US/US]; 574 Holyoke, San Francisco, CA 94134-1737 (US). HRUZEWICZ, Witold, N. [PL/US]; 1503 McKinnon Avenue, San Francisco, CA 94124 (US). KOLESNIKOV, Aleksandr [UA/US]; 1474 46th Avenue, San Francisco, CA 94122 (US). MACKMAN, Richard, Laurence [GB/US]; 2240 Bay Street, Apt. 302, San Francisco, CA 94403 (US). RAI, Roopa [IN/US]; 237 Clifton Avenue, San Carlos, CA 94070 (US). SPENCER, Jeffrey, R. [US/US]; 8 Baycrest Way, South San Francisco, CA 94080 (US). VERNER, Erik, J. [US/US]; 709 Catamaran Street, #1, Foster City, CA 94404 (US). YOUNG,	<b>Wendy, B. [US/US]; 110 West 3rd Avenue #5, San Mateo, CA 94403 (US).</b> <b>(74) Agents:</b> KATHARDEKAR, Vinit, G. et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US). <b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report. <b>(88) Date of publication of the international search report:</b> 26 October 2000 (26.10.00)	
<b>(54) Title:</b> (HETERO)ARYL-BICYCLIC HETEROARYL DERIVATIVES. THEIR PREPARATION AND THEIR USE AS PROTEASE INHIBITORS <b>(57) Abstract</b>  The present invention provides novel compounds of the Formula (I): A-B, its prodrug forms, or pharmaceutically acceptable salts thereof, wherein A represents a saturated, unsaturated, or a partially unsaturated bicyclic heterocyclic ring structure, and B represents an aryl or a heteroaryl group. Preferred compounds of the present invention comprise a benzimidazole or indole nucleus. The compounds of this invention are inhibitors of serine proteases, Urokinase (uPA), Factor Xa (FXa), and/or Factor VIIa (FVIIa), and have utility as anti cancer agents and/or as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.		

(51) International Patent Classification: (continued)

C07D 401/10, 403/10, 471/04, 417/10, 413/10, 407/10, 209/12, 409/10, 407/12, A61K 31/44, 31/425, 31/40,  
C07F 9/09, A61K 31/66 // (C07D 471/04, 235:00, 221:00)

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/30302

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D235/18 A61K31/415 A61P7/02 C07D401/10 A61K31/44  
C07D403/10 C07D471/04 C07D417/10 A61K31/425 C07D413/10  
C07D407/10 C07D209/12 A61K31/40 C07D409/10 C07D407/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TIDWELL R.R. ET AL.: "Diarylamidine derivatives with one or both of the aryl moieties consisting of an indole or indole-like ring. Inhibitors of arginine-specific esteroproteases" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 21, no. 7, 1 July 1978 (1978-07-01), pages 613-623, XP000573913 ISSN: 0022-2623 the whole document -- -/-	4-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

28.06.00

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

Int. nat. Application No

PCT/US 99/30302

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F9/09 A61K31/66 //(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 114, no. 21, 27 May 1991 (1991-05-27) Columbus, Ohio, US; abstract no. 207259j, NISHI T. ET AL.: "Preparation of benzothiazoles and benzimidazoles as blood platelet aggregation inhibitors" page 832; column 1; XP002139445 abstract & JP 02 306916 A (OTSUKA PHARMACEUTICAL CO., LTD.; JAPAN) compounds 86-91 page 148 -page 149; table 2  -/-	4,6,9-11

☒ Further documents are listed in the continuation of box C.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

6 June 2000

Date of mailing of the international search report

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/30302

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IWANOWICZ E.J. ET AL.: "Derivatives of 5-amidine indole as inhibitors of thrombin catalytic activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 6, no. 12, 18 June 1996 (1996-06-18), pages 1339-1344, XP004134837 ISSN: 0960-894X scheme 1 table 1	12,13, 15,16
X	WO 98 22619 A (ARRIS PHARMACEUTICAL CORPORATION & REGENTS OF UNIVERSITY OF CALIFORNIA) 28 May 1998 (1998-05-28) claims 32-44,48,52,54	4-16
P,X	WO 99 26933 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03)  compounds 22, 23 page 34; claims 1-7,9-11	4-7, 9-13,15, 16
A	KATZ B.A. ET AL.: "Design of potent selective zinc-mediated serine protease inhibitors" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 391, 5 February 1998 (1998-02-05), pages 608-612, XP002095430 ISSN: 0028-0836 compounds APD-4, APD-6, APD-8	4-16
P,A	WO 99 26941 A (AXYS PHARMACEUTICALS, INC.) 3 June 1999 (1999-06-03) compounds 1-7, 12-14, 18, 24-26, 28-30, 37, 42, 48-69, 84-88, 103-106, 108-110, 114-117 claims 1-8	4-16

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/30302

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 11 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-3  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3

Due to the fact that the definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups (only partly supported by examples given in the description), the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (cf. Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Therefore the search was performed on the basis of the examples and those claims derived therefrom which are clear and concise, in combination with the alleged pharmaceutical use as protease inhibitors. The search report thus covers those compounds of formula (I) wherein A denotes either a benzimidazole or an indole moiety attached in 2-position to B being a substituted phenyl moiety, see claims 4, 5, 6(part), 7(part), 8, 12, 13 and 14 in combination with claims 11 or 16.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

information on patent family members

Int. onal Application No

PCT/US 99/30302

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2306916 A	20-12-1990	JP 2869561 B	10-03-1999
WO 9822619 A	28-05-1998	AU 2336497 A	10-06-1998
		EP 0943008 A	22-09-1999
WO 9926933 A	03-06-1999	AU 1608399 A	15-06-1999
WO 9926941 A	03-06-1999	AU 1607299 A	15-06-1999